



INTERNATIONAL
SOCIETY
FOR INFECTIOUS
DISEASES

GUIDE TO INFECTION CONTROL IN THE HEALTHCARE SETTING

Antibiotic Resistance

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KEY ISSUES

Begun in the 1940s, the antibiotic era is under 80 years' duration, yet now is challenged by the worldwide increase in the incidence of resistance by microorganisms.

KNOWN FACTS

- It is estimated that 700,000 people globally die from drug-resistant infections yearly. Unless major actions are taken this number is projected to rise to 10 million yearly by 2050 at an economic impact of 100 trillion dollars per year.
- In the community, penicillin-resistant pneumococci and multidrug-resistant tuberculosis (MDR-TB) are major public health problems. These organisms also have become significant nosocomial pathogens.
- In communities and hospitals throughout the world, there are special problems with methicillin-resistant *Staphylococcus aureus* (MRSA). Phenotypically different community-associated MRSA (CA-MRSA) strains now cause many nosocomial and community infections.
- The explosion of infections with vancomycin-resistant *Enterococcus faecium* in hospitals has been remarkable.
- Resistance of Gram-negative rods to quinolones and third generation cephalosporins continues to increase.
- Gram-negative organisms carrying extended-spectrum beta-lactamases (ESBLs) are now common. ESBLs enable bacteria to resist most beta-lactam antibiotics. Such strains are usually susceptible to carbapenems such as imipenem and meropenem.
- With increasing use of carbapenems there has been the emergence of bacteria harboring carbapenemases, beta-lactamases that inactivate

imipenem and meropenem. Some such strains are susceptible only to colistin.

- Colistin resistance via the plasmid-mediated MCR-1 gene has recently been described, raising concern for the development of completely drug-resistant Gram-negative organisms.
- Fluoroquinolone resistance in *Neisseria gonorrhoeae* is widespread. Recently cephalosporin resistant gonorrhea has been described and raises the specter of untreatable infection.
- The emergence of strains of *S.aureus* with intermediate levels of resistance to vancomycin (VRSA) has been noted in several countries. These strains have MICs of 4-8 micrograms/ml. In 2002, two strains of *S.aureus* with high levels of resistance to vancomycin (VRSA) were reported in the United States. These strains have MICs $>$ or $=$ 16 micrograms/ml. As of February 2015, 14 patients in the U.S. have been identified with infections due to VRSA.
- Drug resistance is a major problem in both *Plasmodium falciparum* and *P. vivax*. Chloroquine resistance is widespread globally and some strains of *P. falciparum* have developed resistance to nearly all antimalarial drugs.
- In 2014 an estimated 480,000 people developed MDR-TB with 190,000 deaths.
- The burden of both antimicrobial resistance and healthcare associated infections (HCAI) is high in all low-and middle-income countries (LMICs), where pooled infection data suggest HCAIs rates are at least three times as high as rates in resource-rich countries.
- Counterfeit or fake antibiotics are a problem in many countries. Fake antibiotics might be contaminated, contain the wrong dose or no active ingredient at all and can contribute to generating resistance.

Unless we pay attention to the problem of antibiotic resistance, we will quickly run out of effective therapy. Unfortunately, the problem of resistance comes at a time when fewer pharmaceutical companies are in

the business of developing new antimicrobials. Thus, the pipeline of new drugs is limited.

Controversial Issues

- The causes of antibiotic resistance are not clearly known, but surely **unnecessary use of antibiotics** is important. Such high use leads to the selection of resistant organisms. Once a patient has a resistant organism, then the possibility exists for transmission to other patients. The initiating problem is the selection of a resistant isolate under the “pressure” of antibiotic usage.
- A second issue is excellent **infection control** — isolation and handwashing — to minimize spread of antibiotic resistant isolates. Exactly what proportion of the level of resistance stems from poor infection control is unclear, but is thought to be higher for Gram-positive than Gram-negative organisms.
- The third issue relates to the **influx of patients** harboring resistant strains on admission to the hospital. Thus, the issue is a need for quickly identifying patients and isolating them on admission. This requires labeling the charts of patients previously known to be infected with or carriers of antibiotic-resistant pathogens. When the patient enters the hospital, he or she should be automatically placed in appropriate isolation. It remains unclear at what level of resistance it is no longer cost effective to maintain a program of isolation on admission. The level of resistance in hospitals to antibiotics can be considered to be influenced by three major parameters: how much enters an institution, how much is selected *de novo* or afterwards, and how much spreads as a result of poor infection control. Imagine that one wanted to know what contributed to the current rate of MRSA: It is mostly related to infection control, influenced by the incoming burden of MRSA positive cases, but less so by the quantity of methicillin used. In contrast, the level of

resistant gram-negative rods is very much influenced by antibiotic pressure and the incoming burden of resistant gram-negative rods.

- A fourth issue is the **lack of risk-adjusted global standards** for measuring and reporting antibiotic consumption. Additionally, for many pathogens systematic monitoring for drug resistance does not occur.
- **Antimicrobial Stewardship Programs (ASPs)** are designed to optimize the safe and effective use of antimicrobials and to decrease the emergence of resistance. However, the most optimal ASP structure, activities and outcomes are not known for various settings.

SUGGESTED PRACTICE

Six areas for control of this problem are as follows:

1. Minimize the use of antibiotics to limit the emergence of antibiotic resistance.
2. Maximize good hand washing and isolation practices to limit transmission of any antibiotic-resistant organisms that may emerge in the hospital or enter with a new patient.
3. Develop systems to identify quickly and isolate immediately all new patients who might be carrying an important antibiotic-resistant pathogen. This may be accomplished by marking the charts of patients previously known to be carriers or by isolating all patients coming from another facility known to have a high number of antibiotic-resistant organisms.
4. Monitoring for antibiotic resistance should be performed locally and inform local guidelines for empiric therapy as well as for perioperative prophylaxis.
5. Antimicrobial consumption should be monitored and correlated to local antibiotic resistance patterns whenever possible.

6. Wherever feasible dedicated Antimicrobial Stewardship Programs should be created to spearhead efforts in optimizing local antimicrobial use.

SUGGESTED PRACTICE IN UNDER-RESOURCED SETTINGS:

- If no antimicrobial resistance testing is available:
 - Investing in lab capacity to test for antibiotic resistance is crucial and needs to be a priority at the national level.
 - Without resistance testing, targeted antimicrobial treatment is challenging and will need to be based on clinical symptoms, lab and imaging results and – if available – local or regional resistance data.
- Antibiotics should not be given out without a prescription.
- Access to new antibiotics should be restricted and their use ideally would be directed by susceptibility testing.
- Proper duration of antibiotic therapy based on diagnosis is important. Antibiotic therapy should always have an end date identified by condition.
- Healthcare workers should be trained in adequate infection control practices.

SUMMARY

Antimicrobial resistance is a global public health crisis. Global, coordinated efforts are necessary to preserve the effectiveness of the antimicrobials that are currently available, to prevent infections wherever possible, to create and deploy new testing to detect drug resistance and to create new

antimicrobials. If significant global action is not taken, we risk fully entering a post-antibiotic era.

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Figure 4.1

Tackling Antimicrobial Resistance on Ten Fronts

O'Neill J et al. Tackling Drug Infections Globally: Final Report and Recommendations. 2016; CC BY 4. 0.

TACKLING ANTIMICROBIAL RESISTANCE ON TEN FRONTS



Review on
Antimicrobial
Resistance